IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:

Applicants:	Finkelman *et al.*	:	Case No.	91830/625
Serial No.	09/167,088	:	Examiner:	G. Gabel
Filed:	October 6, 1998	:	Art Unit:	1641

Title: METHODS FOR MEASURING IN VIVO CYTOKINE PRODUCTION

The Assistant Commissioner of Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR 1.132

1. This declaration under 37 CFR Sec. 1.132 is supportive of the Preliminary Amendment filed herewith.

2. I, Ethan M. Shevach, M.D., been employed by the NIH since 1969 , and that from 1971 to the present time he has been, and still is, engaged in a research program in the field of immunology and particularly Cellular Immunology and Cytokine Biology;

3. I have reviewed the 21 December 1999 Office Action in the above captioned case and I am familiar with the references, Tamarkin *et al.* (US 5,328,899), Finkelman *et al.* (Journal of Immunology 151:1235-1244 (1993)), Pouletty *et al.* (US 5,612,034), David *et al.* (US 4,486,530) and Gosling (Clin. Chem. 36(8): 1408-1427 (1990)), cited by the Examiner.

4. I disagree with the Examiner's position and maintain that one of ordinary skill in the field of immunology and medical science would not deduce the present invention upon reading the references cited by the Examiner, either alone or in combination.

5. The assay disclosed by Tamarkin reference is a competitive binding assay that measures the ability of an analyte present in a serum sample to block the binding of biotin-labeled analyte to the plate. The assay measures the total of bound and unbound analyte present in a biological fluid. If the analyte is one with a short biological half-life and is not bound by endogenous serum proteins, the Tamarkin assay binding protein would not contact the analyte at all since it would be used up too quickly in the biological system. If endogenous serum proteins bind the analyte, then the methods of the Tamarkin reference would measure some product of the quantity of the analyte and quantity of analyte binding protein produced over an unknown period of time. Differences in the

quantity of analyte measured in two samples might reflect differences in quantity of analyte binding protein in the samples rather than quantity of analyte produced.

6. Tamarkin differs from the claimed process in that it is a competitive binding assay using polyclonal antibodies adhered to a plate to measure the ability of an analyte present in a serum sample to block the binding of biotin-labeled analyte to the plate. The Tamarkin reference teaches using a single, polyclonal antibody, not two specific binding molecules (preferably monoclonal antibodies); it is not utilized in vivo to obtain the specific amount of analyte excreted over a fixed period of time; it does not teach using an excess of binding molecule; and it does not teach using a neutralizing binding molecule that binds the analyte and prevents its catabolism, excretion, or binding to its respective receptor.

7. The Finkelman *et al.* reference discloses the idea that if one complexes an analyte, such as a cytokine, with an analyte binding protein and then injects the complex, the analyte survives longer in vivo than free or unbound analyte. In the present invention, the novel approach is to inject large quantities of analyte binding molecule so that the analyte binding molecule is in excess in order to favor analyte binding rather than dissociation and allow for more reliable capture and measure of such analyte. The result is that the analyte-binding molecule acts to capture the analyte and blocks utilization versus the association and concurrent slow release of the Finkelman reference.

8. Pouletty *et al.* teaches only that one can increase the in vivo biological half-life of a compound that normally has a short in vivo half-life by injecting it into an animal so that it binds covalently to a molecule that naturally has a long in vivo half-life.

9. David *et al.* teaches only that a two-site or sandwich type assay may be used to determine the presence and concentration of an antigen. There is no mention or suggestion that such an assay may be used to determine analyte production *in vivo*.

10. While Gosling *et al.* teaches the use of an excess of antibody to eliminate differences in affinity, there is no mention or suggestion that such an assay may be used to determine analyte production *in vivo*.

11. In my opinion, one of ordinary skill in the field of immunology and medical science would find nothing in Tamarkin, Finkelman, Pouletty, David, or Gosling alone or in combination that would teach or suggest the present invention or any reason for making it.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Ethan M. Shevach, M.D.

8/15/02

Date: